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Review

Mast cells as therapeutic target in cancer

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ABSTRACT

Mast cells promote tumorigenesis and tumor progression, and have functions that favor the host. Increased mast cell number correlates with a poor prognosis in several human tumors. In different vascular tumors, as well as a number of hematological and solid tumors, mast cell accumulation correlate with increased neovascularization, tumor aggressiveness, and metastatic spread. Mast cells might act as a new target for the adjuvant treatment of tumors through the selective inhibition of angiogenesis, tissue remodeling and tumor-promoting molecules, permitting the secretion of cytotoxic cytokines and preventing mast cell-mediated immune suppression.

Contents

1. The role of mast cells in tumor growth and angiogenesis

Although some evidence suggest that mast cells can promote tumorigenesis and tumor progression, there are some clinical data and experimental tumor models in which mast cells seem to have functions that favor the host (Ribatti and Crivellato, 2009).

Mast cells are attracted in the tumor microenvironment by stem cell factor (SCF) secreted by tumor cells and secrete several angiogenic factors (Table 1) as well as matrix metalloproteinases (MMPs), which promote tumor vascularization and invasiveness, respectively (Ribatti and Crivellato, 2009). Moreover, mast cells release histamine, which modulate tumor growth through H1 and H2 receptors (Fitzsimons et al., 1997). Mast cells exert a dual role in tumor fate through the relase of several mediators (Fig. 1). In more detail, mast cells induce immunosuppression releasing tumor necrosis factor alpha (TNF-α) and interleukin 10 (IL-10), which are involved in promoting the immune tolerance mediated by regulatory T (Treg) cells (Grimbaldeston et al., 2007; Ullrich et al., 2007). On the contrary, mast cells promote inflammation, inhibition of tumor cell growth, and tumor cell apoptosis by releasing IL-1, IL-4, IL-6, IL-8, monocyte chemotactic protein-3 and -4 (MCP-3 and MCP-4), transforming growth factor beta (TGF-β), and chymase.

Increased mast cell number correlates with a poor prognosis in several human tumors, including melanoma (Ribatti et al., 2003b), oral squamous carcinoma (Iamaroon et al., 2003), squamous cell carcinoma of the lip (Rojas et al., 2005), and breast cancer (Groot

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Table 1
Angiogenic factors stored in mast cells.

Adrenomedullin
Chymase
FGF-2
Heparin
Histamine
IL-8
MMP-2
MMP-9
NGF
TGF-β
Tryptase
TNF-α
VEGF

Abbreviations: FGF-2, fibroblast growth factor-2; IL-8, interleukin-8; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; NGF, nerve growth factor; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

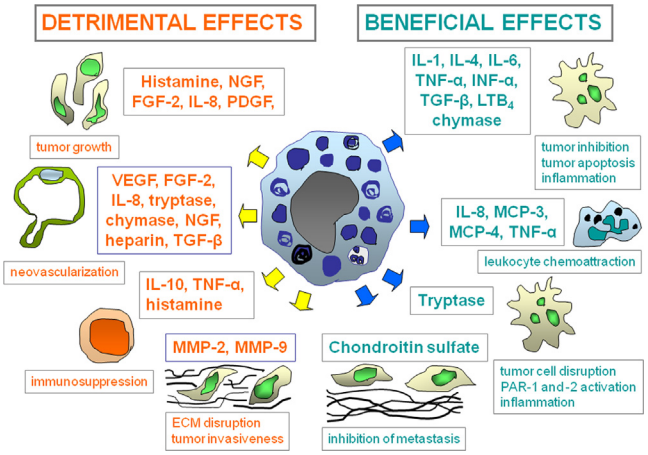

Fig. 1. The dual role of mast cells in tumor fate. Mast cells may release in the tumor stroma cytokines and growth factors, such as FGF-2, NGF, PDGF, IL-10 and IL-8, which have detrimental effects to the host by stimulating tumor cell expansion. Mast cells are a major source of histamine, which can induce tumor cell proliferation through H1 receptors, while suppressing the immune system through H2 receptors. In addition, mast cells synthesize and store angiogenic factors as well as matrix metalloproteinases, which promote tumor vascularization and tumor invasiveness, respectively. Mast cells may also generate immunosuppression by releasing IL-10, histamine and TNF-α. By contrast, mast cells may promote inhibition of tumor cell growth, tumor cell apoptosis and inflammation by releasing cytokines such as IL-1, IL-4, IL-6, and TNF-α. TNF-α, in particular, is very effective in leukocyte chemoattraction. Chondroitin sulfate may inhibit tumor cell diffusion and tryptase causes both tumor cell disruption and inflammation through activation of protease-activated receptors (PAR-1 and -2). Abbreviations: FGF-2, fibroblast growth factor-2; NGF, nerve growth factor; PDGF, platelet derived growth factor; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; INF-α, interferon-α; LTB_4, leukotriene B4; MCP-3, MCP-4, mast cell protease-3, -4; MMP-2, MMP-9, matrix metalloproteinase-2, -9 (Reproduced from Ribatti and Crivellato (2011)).

Kormelink et al., 2014). Otherwise, increased mast cell number correlates with host antitumor effect in skin tumor development (Siebenhaar et al., 2014).

Mast cells produce several pro-angiogenic factors and migrate *in vivo* and *in vitro* in response to VEGF and placental growth factor-1 (PlGF-1) (Detoraki et al., 2009). Human lung mast cells express VEGF-A, VEGF-B, VEGF-C and VEGF-D, and supernatants of activated lung mast cells induced an angiogenic response in the chick embryo chorioallantoic membrane (CAM) assay, inhibited by an anti-VEGF-A antibody (Detoraki et al., 2009). Parallely, granulated murine mast cells and their granules stimulate a strong angiogenic reaction in the CAM assay, partly inhibited by anti-FGF-2 and –VEGF antibodies (Ribatti et al., 2001). Intraperitoneal injection of the degranulating compound 48/80 causes an angiogenic response in the rat mesentery window angiogenic assay and in mice (Norrby et al., 1986, 1989). Finally, histamine and heparin stimulate proliferation of endothelial cells *in vitro* and are angiogenic in the CAM assay (Ribatti et al., 1987; Sorbo et al., 1994).

Mast cells store in their secretory granules pre-formed active serine proteases, including tryptase and chymase (Metcalfe et al., 1997). Tryptase stimulates the proliferation of endothelial cells, promotes vascular tube formation *in vitro*, degrades connective tissue matrix, and activates MMPs and plasminogen activator (PA), which induce the release of VEGF or FGF-2 from their extracellular matrix-bound state (Blair et al., 1997), and is angiogenic *in vivo* in the CAM assay (Fig. 2) (Ribatti et al., 2011). The expression of mast cell chymase and tryptase correlated with mast cell maturation and angiogenesis during tumor progression in BALB/c mouse (de Souza et al., 2012). Mast cells contain MMPs, and tissue inhibitors of metalloproteinases (TIMPs), (Koskivirta et al., 2006; Tanaka et al., 2001) which intervene in regulation of extracellular matrix degradation, allowing release of angiogenic factors. Mast cell-deficient W/Wv mice exhibit a decreased rate of tumor angiogenesis (Starkey et al., 1988). Development of squamous cell carcinoma in a human papilloma virus (HPV) 16 infected transgenic mouse model of epithelia carcinogenesis provided experimental support for the participation of mast cells in tumor growth. Mast cells infiltrate the stroma of the invasive front of carcinomas, proximal to capillaries (Coussens et al., 1999). Infiltration of mast cells and activation of MMP-9 parallels the angiogenic switch in premalignant lesions through the release of pro-angiogenic molecules from the extracellular matrix. Angiogenic switch is absent in a mast cell-deficient HPV 16 transgenic mouse indicating that infiltration of mast cells in the skin is necessary for tumor progression (Coussens et al., 1999, 2000). In prostate tumors derived from both tumor transgenic adenocarcinoma of the mouse prostate (TRAMP) mice and human patients, mast cells promote well-differentiated adenocarcinoma growth (Pittoni et al., 2011b).

In different vascular tumors, like haemangioma and haemangioblastoma (Glowacki and Mulliken, 1982), as well as a number of hematological and solid tumors, including lymphomas (Fukushima et al., 2001; Ribatti et al., 1998), multiple myeloma (Ribatti et al., 1999), myelodysplastic syndrome (Ribatti et al., 2002), B-cell chronic lymphocytic leukemia (Molica et al., 2003), breast cancer (Bowrey et al., 2000; Hartveit, 1981; Ribatti et al., 2007), squamous cell cancer of the esophagus (Elpek et al., 2001), gastric cancer

Fig. 2. Tryptase is angiogenic *in vivo* in the CAM assay. Macroscopic pictures of CAM at day 12 of incubation, treated with tryptase. Note the presence of numerous blood vessels converging toward the implant. Modified from Ribatti et al. (2011).